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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/535,746	05/20/2005	Judah Folkman	701039-055264	9640

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EXAMINER	
WOOD, AMANDA P	
ART UNIT	PAPER NUMBER
1657	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/535,746	FOLKMAN ET AL.	
	Examiner	Art Unit	
	AMANDA P. WOOD	1657	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *13 December 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,5,8-19,22,30,35 and 36* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,5,8-19,22,30,35 and 36* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *20 May 2005 and 09 September 2005* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *4/06, 10/06*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

Applicant's election filed on 13 December 2007 has been received and entered. Based upon Applicant's arguments and further review of the application and instant claims, the election of species requirement has been withdrawn.

Claims 1, 5, 8, 9-19, 22, 30, and 35-36 are presented for consideration on the merits.

Priority

The current application filed on May 20, 2005 is 371 of PCT/US05/14210 filed April 26, 2006. Applicants' claim of priority to earlier filed provisional applications needs to be adequately inspected and addressed in the future office actions since the information provided by the applicants is not consistent with the PTO data base, see amendment to the spec filed May 20, 2005.

Preliminary Amendment

The preliminary amendment filed May 20, 2005 has been entered.

Drawings

Drawings filed May 20, 2005 and September 9, 2005 have been accepted.

Information Disclosure Statement

The IDS filed April 19, 2006 and September 18, 2006 have been received and are signed and considered, a copy of the PTO 1449 is attached to the following document.

Claim Objections

Claim 1 is objected to because of the following informalities: PF-4 in line 4 of claim 1 should be spelled out the first time it appears in the claim. Appropriate correction is required.

Claim 30 is objected to because of the following informalities: "Chrohn's disease" is misspelled in line 6. Appropriate correction is required.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1, 5, 8, 9-19, 22, 30, and 35-36 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1, 2, 5-16, and 24-27 of copending Application No. 11/304384. Although the conflicting claims are not identical, they are not patentably distinct from each other because the

claims of the instant application are drawn to isolating platelets at two different time points, analyzing levels of angiogenic regulator PF4 at each time point, and then comparing the levels at the two different time points. The claims of the instant application are further drawn to determining at least a second angiogenic regulator in the platelets. The claims of the '384 application are drawn to isolating platelets at two different time points, analyzing levels of at least two different angiogenic regulators (of which PF4 is one choice) at each time point, and then comparing the levels at the different time points. The claims of both applications are drawn to determining the angiogenic regulator levels in individuals having a genetic predisposition to cancer, having particular tumor suppressor genes, and those with particular types of cancer or other angiogenic diseases.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 5, 8, 9-19, 22, 30, and 35-36 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable

one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The factors to be considered in determining whether undue experimentation is required are summarized In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir.1988). The court in Wands states: "Enablement is not precluded by the necessity for some experimentation such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue,' not 'experimentation.' "(Wands, 8 USPQ2d 1404). Clearly, enablement of a claimed invention cannot be predicated on the basis of quantity of experimentation required to make or use the invention. "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations." (Wands, 8 USPQ2d 1404). The factors to be considered in determining whether undue experimentation is required include: (1) the breadth of the claims, (2) the nature of the invention, (3) the state of the prior art, (4) the predictability or unpredictability of the art, (5) the relative skill of those in the art, (6) the amount or direction or guidance presented, (7) the presence or absence of working examples, and (8) the quantity of experimentation necessary.

N.B. MPEP 2164.04 states, "[w]hile the analysis and conclusion of a lack of enablement are based on the factors discussed in MPEP § 2164.01(a) and the evidence as a whole, it is not necessary to discuss each factor in the written enablement rejection" and that "[t]he language should focus on those factors, reasons, and evidence that lead the examiner to conclude that the specification fails to teach how

to make and use the claimed invention without undue experimentation, or that the scope of any enablement provided to one skilled in the art is not commensurate with the scope of protection sought by the claims." Accordingly, the Factors most relevant to the instant rejection are addressed in detail below.

1-2 .Breadth of the claims and the nature of the invention..

In regards to the method of the invention and the breadth of the claims the broadest interpretation that applies is a method that detects angiogenic disease or disorder by comparing PF-4 levels from isolated platelets at two different time points in individuals.

3-4. The state of prior art and the level of predictability in the art.

The prior art indicates that PF-4 inhibits angiogenesis and that regions of active angiogenesis in vivo preferentially bind rhPF-4 (see, for example, Hansell et al 1995). Furthermore, Borgstrom teaches that fluorescently labeled PF-4 intensely and specifically labeled capillaries growing into implanted breast tumors, and that human breast cancer cell lines possess considerable angiogenic activity (see, Borgstrom 2003). Borgstrom further teaches that there is currently no reliable information on in vivo angiogenic behavior of breast cancer, and that the results of the PF-4 labeling study in breast cancer were a prerequisite for the evaluation of PF-4 as an angiogenic marker.

5. The relative skill in the art.

The relative skill in the art as it relates to the method of the invention is characterized by that of a M.D. or Ph. D. level individual.

6-7. The amount of guidance present and the existence of working examples.

Applicant does not provide any working examples in the instant specification regarding analyzing platelets for levels of PF-4 and comparing the levels of PF-4 from a first time point to a second time point wherein a change in the level of PF-4 in the platelets from the second time point indicates an angiogenic disease or disorder. Applicant provides no guidance as to what "a change" in the level of PF-4 means, and furthermore, Applicant does not relate PF-4 directly to cancer in general, breast cancer or to the tumor suppressor gene BRCA1. In addition, Applicant has not provided examples wherein the second time point is at least 6 months, 10 months or one year after the first time point with regard to PF-4. Furthermore, Applicant does not provide any working examples or guidance for a method of analyzing platelets for PF-4 and at least one additional angiogenic regulator, wherein a change in the level of PF-4 or the additional angiogenic regulator indicates an angiogenic disease or disorder.

8. The quantity of experimentation necessary.

The amount of experimentation that is required is undue: while isolating platelets and analyzing the level of PF-4 is routine, a method of further comparing the levels of PF-4 at first and second time points to determine a change in levels for indication of an angiogenic disease or disorder is not routine and requires more experimentation. Therefore, in view of the overly broad scope of the claims, the lack of guidance and working examples provided in the specification, and the high degree of unpredictability as evidenced by the prior art, undue experimentation would be

necessary for a skilled artisan to make and use the entire scope of the claimed invention.

All other claims depend directly or indirectly from rejected claims and are, therefore, also rejected under USC 112, first paragraph for the reasons set forth above.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 30 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 30 recites the limitation "retinopathy, diabetic retinopathy, macular degeneration, restenosis, inflammatory disease, arthritis, rheumatoid arthritis, psoriasis, Crohn's disease, benign tumors, hemangiomas, neurofibromas, and granulomas" in lines 5-7. There is insufficient antecedent basis for these limitations in the claim (i.e., these limitations are not "cancers" as required by the Markush language of the claim in line 1.

Claim 8 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. In particular, claim 8 recites the phrase "wherein the platelets are analyzed for the presence of at least one angiogenic regulator" in lines 1-2. It is unclear from the phrasing of the claim whether this claim is intended to add an

additional step to claim 1, or whether it is intended to simply further limit the steps of analyzing platelets in claim 1. If claim 8 is intended to further limit the analyzing steps of claim 1, the language of claim 8 does not make it clear that this is the case, since the language in claim 1 is narrower that the broad terms of claim 8 (i.e., analyzing level of PF-4 versus the presence of a generic angiogenic regulator, respectively).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1, 5, 8, 12, and 13 are rejected under 35 U.S.C. 103(a) as being unpatentable over Komurasaki et al (US 5,847,084).

A method is claimed for the detection of an angiogenic disease or disorder in an individual comprising the steps of isolating platelets at a first time point, analyzing said platelets for the level of PF-4, isolating platelets at a second time point, analyzing said platelets for the level of PF-4, and comparing the levels of PF-4 from the first time point to the levels of PF-4 from said second time point.

Komurasaki et al beneficially teach a method of isolating platelets from blood samples and then eluting PF-4 from the platelets. Furthermore, Komurasaki et al beneficially teach that Western blotting can be used to quantify the PF-4 obtained from the platelets. In addition, Komurasaki et al teach that PF-4 has angiogenesis inhibitory activity in malignant tumors and that it has been effective for suppressing malignant

tumor cells(see, for example, col. 1, lines 45-67, col. 3, lines 20-65 and col. 4, lines 20-45).

It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to modify the methods of isolating platelets and PF-4 as disclosed by Komurasaki et al, based upon the art-recognized method of monitoring patients' health conditions by comparing values of particular health parameters taken at one time point to those taken at a second time point. The result-effective adjustment of particular conventional working conditions (e.g., using a particular means to isolate platelets and to analyze the level of PF-4 in the platelets) is deemed merely a matter of judicious selection and routine optimization which is well within the purview of the skilled artisan.

From the teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole, was *prima facie* obvious to one of ordinary skill in the art at the time the claimed invention was made, as evidenced by the cited references, especially in the absence of evidence to the contrary.

Conclusion

No claims allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to AMANDA P. WOOD whose telephone number is (571)272-8141. The examiner can normally be reached on M-F 8:30AM -5PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jon Weber can be reached on (571) 272-0925. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

APW
Examiner
Art Unit 1657

/Robert B Mondesi/
Primary Examiner, Art Unit 1652